GUIDE TO BIORESEARCH MONITORING INSPECTIONS

OF IN VITRO DIAGNOSTIC DEVICES

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INTRODUCTION

The purpose of this document is to provide

a written reference for Food and Drug

Administration (FDA) Investigators conducting bioresearch monitoring (BIMO) inspections involving in vitro diagnostic (IVD) devices. The following material presents key aspects of existing compliance approaches to BIMO IVD inspections.

This guide was prepared by the FDA, Office of Regulatory Affairs (ORA) and the Center for Devices and Radiological Health (CDRH) with input from the Center for Biologics Evaluation and Research (CBER).

NATURE, SCOPE, AND PURPOSE

The purpose of bioresearch monitoring inspections is to ensure that data and information contained in premarket applications are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations. Legal authority for these inspections is found in Section 704 of the Federal Food, Drug and Cosmetic Act (the Act) which gives FDA authority to inspect facilities

where devices are "held."

DEFINITION

IVD products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h) of the Act.

EXEMPTIONS FROM 21 CFR 812

Section 21 CFR 812.2(c)(3) exempts investigations of IVD devices from the specific regulations of 21 CFR 812, Investigational Device Exemptions, under certain conditions. Furthermore, because these are clinical investigations, good laboratory practices (GLP) regulations do not apply and should not be used as a basis for citations on the form FDA-483. Although the design control section of the Quality System Regulation applies to

investigational devices, Quality System Regulation deviations should only be cited during Quality System Regulation inspections. In order to be exempt from 21 CFR 812 the sponsor must comply with the labeling requirements of 21 CFR 809.10(c) and the testing requirements of 21 CFR 812.2(c)3).

LABELING REQUIREMENTS

IVDs shipped solely for research purposes must be labeled: "For Research Use Only, Not for use in diagnostic procedures." If an IVD is labeled "For Research Use Only," the research that may be performed is limited to the laboratory research phase needed to identify test kit methods, components, and analytes to be measured. An IVD labeled for research use as described above is mislabeled if used for a clinical study for even one patient if the results are reported to the patient's physician or to the patient's medical records. Research use devices are not to be used to assess the patient's condition regardless of whether or not a confirmatory test or procedure is used.

IVDs shipped for clinical investigations must be labeled: "For Investigational Use Only. The performance characteristics of this product have not been established. The regulations define an investigation as a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device. (See draft CPG Commercialization of In Vitro Diagnostic (IVD) Devices Labeled for Research Use Only or Investigational Use Only, dated January 5, 1998. This CPG will not be implemented until finalized).

PROHIBITED LABELING INFORMATION

Labeling cannot include any representation that the IVD is safe or effective because this is a determination that only the FDA can make based on the review of data gathered through the clinical investigation and supplied by the sponsor to FDA.

Labeling cannot include performance characteristics or expected range because they will be established by the research and/or clinical investigation.

SPECIMEN TESTING AND SAMPLING REQUIREMENTS

The testing must be noninvasive, must not require an invasive sampling procedure that presents significant risk, must not introduce energy into the patient, and must not be used as a diagnostic procedure without confirmation of the diagnosis by an established diagnostic product or procedure.

21 CFR 812.3(k) defines noninvasive devices or procedures as those that do not penetrate or pierce the skin, mucous membranes, ocular cavity or urethra or do not enter body orifices beyond specified limits. However, the regulation defines simple venipuncture to obtain blood specimens and the use of surplus samples of body fluids or tissues left over from samples taken for non-investigational purposes as noninvasive.

Procedures like amniocentesis, lumbar puncture, and tissue biopsy, are examples of invasive sampling procedures that present significant risk. If they are performed solely for the investigation, then the IVD would not be

exempt from the IDE regulations. If samples from these procedures are left over from samples originally taken for non-investigative purposes, then the sampling is considered noninvasive. However, the initial procedure should have been indicated for the patient's condition by current medical practice and not performed to obtain specimens surreptitiously for the clinical investigation.

In order to be exempt from 21 CFR 812, the investigational device cannot be used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure. Disease diagnosis usually involves a number of observations and factors including signs and symptoms, medical history, and a battery of tests. There are few tests that are pathognomonic, i.e., are considered "gold standards," for diagnosis of a disease and, therefore, the diagnosis is established from a number of factors. Moreover, a sponsor or investigator may consider the investigational

IVD to be more accurate, precise, sensitive, specific, etc., than current medically established products or procedures. This is generally the goal for producing a new product. Nevertheless, the diagnosis itself must be confirmed in the established way to meet the requirements for exemption from the IDE regulation.

THE SPONSOR'S INVESTIGATIONAL PLAN

In order to obtain valid scientific data to support its submission to the FDA and to maintain the integrity of that data, the sponsor should have an investigational plan including a protocol or other effective means to communicate procedures, etc., to its investigators. Non-adherence to such a protocol should be noted on an FDA 483.

Purpose:

The purpose of the plan is to establish and support claims and information in proposed labeling, including intended use; statements about reagents, instruments, and specimens; the procedure; limitations of the procedure;

expected values; and specific performance characteristics; and to support a determination of safety and effectiveness and/or substantial equivalence.

Description:

Such a study must be carried out in a scientifically sound manner. Therefore, to assure useful results and the integrity of the data and to be able to present their plan to an Institutional Review Board (IRB), the sponsor should develop an investigational plan. A good plan will include all information, procedures, reporting forms, etc., required by the clinical investigator to gather valid data for the sponsor to submit to FDA. These would include such things as a statement of purpose, a protocol, a description of the device, monitoring procedures, labeling, consent materials, IRB information, and additional records and reports. Additional records could include a certification program that ensures that the sponsor is controlling the distribution of the investigational and/or research device and is using it in

scientifically sound research and investigations.

The investigator should sign an investigator's agreement acknowledging his/her responsibilities.

At this phase there should be no promotional/advertising material.

Advertisements to recruit subjects should be reviewed by the IRB to ensure that information is not misleading and that patient's rights and welfare are protected.

IRB and Informed Consent:

The IRB must review and approve the protocol and consent materials before the study can begin. 21 CFR 56, Institutional Review Boards, and 21 CFR 50, Informed Consent, do not specifically exempt IVDs and, therefore, are applicable.

Because most IVD research and investigations do not require an IDE and are minimal risk, the IRB may use expedited review procedures to review most IVD research and investigational proposals. The IRB must document why expedited review was used for

approving the IVD investigation.

The IRB may exempt the study from informed consent if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required. For example, an IRB may exempt a study from informed consent if left-over specimens will be used, provided that patient confidentiality is maintained.

Protocol:

While the protocol does not need FDA approval, it is an essential tool for the sponsor to communicate accurately to the IRB and the clinical investigator. Although the sponsor is exempt from labeling requirements if it meets the requirements of 21 CFR 809.10(c), the labeling or its equivalent supplies the clinical investigator with important information about the test procedure. Without a protocol, or similar tool, the sponsor runs the risk of getting invalid results from the investigation.

The protocol and the labeling should reflect

all the steps the clinical investigator must take to obtain useful information for the sponsor. They should describe such things as specimen collection, instrumentation, reagents, calibration, quality control, step-by-step procedures, calculations, storage conditions, stability of various components both before and after opening and/or reconstituting, reporting procedures, and the necessary reporting forms, etc., for obtaining accurate and precise results and communicating them to the sponsor.

PROPOSED INTENDED USE OF THE IVD AND THE CLINICAL DATA

For Diagnosis or Differential Diagnosis of a Disease or Medical or Physiological Condition:

The sponsor may use the data to establish expected values or ranges and cut-off values. The sponsor's proposed labeling will designate concentrations that characterize the healthy and affected populations. These are usually expressed as diagnostic cut-off values. This information will determine the clinical usefulness of the test results and will affect the rates of true and false results. Since treatment

may be based on a diagnosis from an IVD, expected values should be established with accurate information. For example, an IVD to measure blood glucose levels will have a normal range for healthy individuals. Values outside the normal range will be used in the diagnosis of diabetes.

In many cases, the sponsor may simply compare the performance of the investigational device to a device already cleared with the same intended use, using left-over patient specimens. When the patient's diagnosis is necessary, it must have been established by some medically acceptable scientific method. In those cases, the sponsor and investigator must record enough of the patient's medical history to determine the diagnosis and any other conditions that might impinge on the performance of the IVD.

To Monitor a Patient's Therapy or to Follow Their Progress After Treatment:

Records should establish which patients are on the therapy or have had the treatment. For

example, if the IVD measured a tumor marker to assure total removal of the tumor and/or monitor its reoccurrence, then records should reflect the patient's diagnosis and treatment and the pre-treatment levels of the marker.

Screening and Prognosis:

Screening is performed to identify risk factors in health promotion and disease prevention. For example, cholesterol screening may be performed on a random population to identify individuals with this risk factor for heart disease.

Prognosis means determining the intensity or stage of a disease and predicting the expected course of a disease.

Generally firms do not develop an IVD specifically for screening or prognosis. IVDs intended to diagnose or monitor are used instead and the results translated into screening or prognostic terms. If the intended use is, or includes screening, then the investigation should reflect the anticipated screening population, generally healthy adults. If it is for prognosis,

then the screening population should consist almost exclusively of those with the disease.

Prognostic claims should be established with patient outcome data.

Home Use and Physician Office Lab Devices Versus Professional Lab Devices:

If a device is intended for use outside the professional laboratory setting, the Office of Device Evaluation may require other types of studies, e.g., analyses performed by the actual users.

The FDA investigator should be alert to any special instructions, e.g., patient instruction and preparation, when he or she is inspecting such studies.

PERFORMANCE CHARACTERISTICS AND THE CLINICAL DATA

Labeling:

The sponsor may use the investigational data to support the performance characteristics section of the product's proposed labeling. This section of the labeling describes how well the device performed during the clinical investigation and describes such things as the

accuracy, precision, sensitivity, and specificity of the IVD. The sponsor is establishing the purported quality of the device and therefore should assure that the data are valid.

Accuracy or bias describes how well the IVD result compares to the actual concentration in the patient's specimen.

Precision describes how well the IVD repeats test results on the same material.

Sensitivity describes the lowest concentration at which the IVD gives acceptable results.

Specificity is the ability of the IVD to accurately measure the analyte of interest in the presence of potential interfering substances.

The performance characteristics should be related to a generally accepted method and use biological specimens from normal and abnormal populations. The sponsor should define these populations. Too few patients in any one group may not provide the sponsor with the statistical power to make a claim in their labeling.

FACTORS AFFECTING THE QUALITY OF THE RESULTS OF THE CLINICAL INVESTIGATION

There are many factors that may affect the quality and validity of the data collected to support the claims and statements discussed above. The sponsor and investigator should control these factors using QC and QA methods applicable to diagnostic and analytical laboratories. These factors are usually categorized as pre-analytical, analytical, and post-analytical.

Factors:

Pre-analytical considerations center around the patient, his or her preparation, and the specimen.

Analytical considerations include everything surrounding the actual measurement process.

Post-analytical considerations center around the proper calculation and reporting of results.

Although elements of QC and QA principles outlined in FDA's Good Laboratory Practices or Quality Systems GMP Regulation may apply, the regulations themselves do not.

FDA Investigators should base any inspectional observations on whether the sponsor or clinical investigator followed the protocol and labeling specified for the investigation.

Although 21 CFR Part 812, Investigational Device Exemptions (IDE), is used as guidance when reviewing inspectional reports, the IDE regulations themselves do not apply to in vitro diagnostic devices and should not be used as a reference when documenting observations on the FDA-483.

CONCLUSION

In summary, IVDs for clinical investigations or research must meet the labeling requirements in 21 CFR 809.10(c). Labeling must not contain performance claims, diagnostic ranges, indications of safety and effectiveness, etc. The sponsor must control the distribution of the device to avoid the appearance of commercializing an uncleared or unapproved medical device. They must also meet the requirements of 21 CFR 56, Institutional Review Boards, and 21 CFR 50,

Protection of Human Subjects. Additionally, if a protocol or its equivalent exists, the FDA Investigator should assure that the clinical investigator has followed it. The clinical investigator should have followed the specific inclusion and exclusion criteria for patients assuring that the diagnosis for each patient is accurate by a cleared IVD or other standard of diagnosis. They should assure the integrity of the data, specifically, that the analyses were actually performed according to instructions that accompany the kit and that the data were recorded and reported accurately. Raw data should exist to support the data submitted in reports and applications to the Agency.

Although many of these requirements resemble GLPs, the observations should be in terms of adherence to the sponsor's protocol.

Should you have comments or questions regarding In Vitro diagnostic bioresearch monitoring inspections or this guide, please contact Robert Fish at: Center for Devices and Radiological Health Office of Compliance

Division of Bioresearch Monitoring Program

Enforcement Branch II, HFZ-312 28 Gaither

Road Rockville, MD 20850 (301) 594-4723

REFERENCES

This reference is intended to be used in

conjunction with the:

-Compliance Program Guidance Manuals for

Institutional Review Boards; Sponsors,

Contract Research Organization and

Monitors; and Clinical Investigators (CP

7348.809; 7348.810; and 7348. 811),

-21 CFR Part 809 - In Vitro Diagnostic

Products for Human Use

-21 CFR Part 812.2 (c)(3), 812.3(k) - IVD

exemptions

-21 CFR Part 50 - Protection of Human

Subjects

-21 CFR Part 56 - Institutional Review

Boards

-Investigations Operations Manual (IOM),

and

-Applicable Compliance Policy Guides

(CPG) for devices (beginning with the

numbers 7124 and 7133).

Guidances are posted to the CDRH and

ORA Internet World Wide Web Home Pages

at http://www.fda.gov. See IOM Chapter 10,

References, for additional information.
